

Neurocognitive performance and serial intravenous subanesthetic ketamine in treatment-resistant depression



Paulo R. Shiroma^{1,2}, C. Sophia Albott^{1,2}, Brian Johns^{2,3}, Paul Thuras^{1,2}, Joseph Wels⁴ and Kelvin O. Lim^{1,2}

¹ Mental Health Service Line, Minneapolis VA Medical Center, Minneapolis, MN, USA

² Department of Psychiatry, University of Minnesota Medical School, Minneapolis, MN, USA

³ Department of Psychiatry, North Memorial Medical Center, Minneapolis, MN, USA

⁴ Department of Anesthesiology, Minneapolis VA Medical Center, Minneapolis, MN, USA

Abstract

The N-methyl-D-aspartate glutamate receptor antagonist ketamine has demonstrated rapid antidepressant effects in treatment-resistant depression (TRD). However, evaluation of ketamine's neurocognitive aspects in TRD has started to be explored. This study aims to (1) examine baseline neurocognitive performance and change in severity of depressive symptoms through six ketamine infusions, (2) examine the neurocognitive effects after completion of serial infusions and whether changes were associated to relapse to depression. Six IV infusions of 0.5 mg/Kg ketamine over 40 min were conducted on a Monday–Wednesday–Friday schedule during a 12-d period on 15 patients with TRD followed by a 4-wk observational period. Neurocognitive functioning was assessed using the CogState battery at baseline and at each follow-up visit. Tasks were designed to test attention, memory (working, visual, and verbal), speed of processing, and set shifting. The likelihood of response through six infusions was greater among depressed subjects with lower attention at baseline ($F(1,13)=5.59$, $p=0.034$). Significant improvement was found in scores of visual memory ($F(4,33.82)=5.12$, $p=0.002$), simple working memory ($F(4, 24.85)=3.29$, $p=0.027$) and complex working memory ($F(4, 32.76)=4.18$, $p=0.008$) after the last ketamine infusion. However, neurocognitive changes were accounted for by improvement in the severity of depressive symptom. The acute neurocognitive effect after completion of repeated infusions was not associated with the likelihood of subsequent relapse during follow-up. Our findings suggest a potential baseline neurocognitive predictor of ketamine response and the apparently lack of short-term neurocognitive impairment after completion of six ketamine infusions in TRD.

Received 1 April 2014; Reviewed 5 May 2014; Revised 19 May 2014; Accepted 21 May 2014

Key words: glutamate, ketamine, treatment-resistant depression, veterans.

Introduction

Ketamine, a non-competitive, high-affinity antagonist of the N-methyl-D-aspartate (NMDA) type glutamate receptor used for induction and maintenance of anesthesia (Green and Li, 2000), has been recently investigated for its high efficacy and rapid antidepressant effect. However, side effects of ketamine have raised some concerns. In 2013, the United Kingdom government upgraded ketamine from a Class C drug to a Class B drug based on recommendations from the Advisory Council on the Misuse of Drugs concerning bladder

damage on ketamine drug users with 'more research needed on the long-term neurocognitive effects'.

Studies in healthy subjects suggested that subanesthetic doses of ketamine as a psychopharmacologic probe disrupt information encoding that occurs during drug administration but does not impair recall for previously learned information (Morgan et al., 2004; Krystal et al., 2005). Other studies have found evidence for selective impairments in aspects of executive functioning (Krystal et al., 1994b; Morgan et al., 2009), while no impairments have been reported (Morgan et al., 2004; Parwani et al., 2005). Ketamine administration at subanesthetic doses appears to carry a very low risk of adverse events in experimental psychopharmacology studies (Perry et al., 2007). These findings are consistent with the lack of long-term effects reported with anesthetic doses of ketamine (Corssen et al., 1971; Moretti et al., 1984).

Given recent interest of ketamine use in treatment-resistant depression (TRD), the neurocognitive effects has just started to be explored. Murrough and

Address for correspondence: Paulo R. Shiroma, Mental Health Service Line, Minneapolis VA Medical Center, Minneapolis, MN, USA and Department of Psychiatry, University of Minnesota Medical School, Minneapolis, MN, USA.

Tel.: +1 612 467 2264 Fax: +1 612 467 4010

Email: paulo.shiroma@va.gov

colleagues (Murrough et al., 2013b) reported impairments in memory recall immediately after a single ketamine infusion was completed. The strategy of repeated ketamine infusions suggest that more than a single infusion achieve better antidepressant outcomes (Murrough et al., 2013a; Rasmussen et al., 2013; Shiroma et al., 2014); however, the short-term neurocognitive effects after completion of treatment are not known.

This study aims to (1) examine the association of baseline neurocognitive performance and the change in severity of depressive symptoms through six consecutive infusions among TRD subjects, (2) examine the neurocognitive effects of serial ketamine infusions during follow-up and whether changes in neurocognition were associated to relapse from antidepressant response.

Methods

Participants

Adult subjects participated in an open-label study of repeat ketamine infusion conducted over 12 d at the Special Diagnostic and Treatment Unit (SDTU) of the Minneapolis VA Medical Center followed by a 4-wk follow-up period. Subjects were recruited by direct referral from clinicians in the Mental Health and Primary Care Clinics. Participants were men and women aged 18 to 70 years with recurrent Major Depressive Disorder (MDD) without psychotic features confirmed by a Structured Clinical Interview for DSM-IV (SCID) (First et al., 1996). Severity of depressive symptoms was defined by a 17-item Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960) score greater than or equal to 14. Patients were considered with TRD if symptoms from current major depressive episode (MDE) failed to improve from at least two adequate antidepressant trials of different pharmacological classes. A systematic evaluation of antidepressant trials was assessed by the Antidepressant Treatment History Form (rating antidepressant trial ≥ 3 ; confidence rating ≥ 3) (Sackeim, 2001). If present, current pharmacological antidepressant dosages including augmenting agents were stable for at least 2 months prior to beginning the study.

Patients were excluded owing to inability to speak English; inability or unwillingness to provide written informed consent; moderate to severe cognitive impairment defined by Mini Mental State Examination (MMSE) (Folstein et al., 1975) scores ≤ 26 ; current or lifetime diagnosis of post-traumatic stress disorder, acute stress disorder, psychosis-related disorder, bipolar disorder I or II disorder, substance-induced disorder, any mood disorder owing to a general medical condition or any Axis I disorder other than MDD that was judged to be the primary presenting problem; diagnosis of Parkinson's disease, dementia of any type, multiple sclerosis, seizures or other central nervous system (CNS)-related disorders; history of moderate/severe traumatic brain injury; comorbid

substance use, abuse or dependence within 6 months of assessment plus negative urine toxicology screen test; clinically unstable medical illness including but not limited to history of or current myocardial ischemia or arrhythmias, severe pulmonary secretions, history of or current closed angle glaucoma, congestive heart failure or angina, significant renal or hepatic impairment, scheduled elective surgery or other procedures requiring general anesthesia during the study, uncontrolled hypertension; current use of barbiturates or narcotic medications; pregnancy (confirmed by baseline lab test), the initiation of female hormonal treatments within 3 months of screening, or inability or unwillingness to use a medically accepted contraceptive method for the duration of the study; active suicidal ideation judged to cause imminent danger.

Baseline assessments were ascertained within one week of first ketamine infusion. The Minneapolis VA Medical Center Institutional Review Board approved the study, and written informed consent was obtained from all subjects before participation. Steps to minimize coercion or undue influences included information about voluntary participation and withdrawal during the study, information on risks and benefits, and ample opportunities for discussion. The investigational aspect of ketamine for TRD was highlighted during the consent process namely that no further ketamine treatment would be provided beyond the study period. All participants were advised to discuss available clinical interventions to treat TRD with their primary psychiatrist after completing the study. Patients were financially compensated for their participation.

Rating scales and procedures

Study design

Participants completed six IV infusions of ketamine on a Monday–Wednesday–Friday schedule over a 12-d period. Patients who met response criteria by the last dose of ketamine were followed weekly for 4 consecutive weeks or until relapse was observed. During this follow-up period, patients continued with similar dosages from pre-study antidepressant regimen. Response was defined as $\geq 50\%$ improvement from baseline depression score as measured by the Montgomery–Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979). Remission was established by a MADRS score ≤ 9 . Relapse was defined as $<50\%$ of baseline MADRS score at that follow-up visit.

Infusion procedures

On the day of infusion, subjects arrived in the morning after an overnight fast. An indwelling catheter was placed in the non-dominant arm for ketamine administration. Digital pulse oxymetry, respiratory rate, heart rate, and blood pressure was recorded every 10 min for 1 h beginning 10 min before infusion. Based on the dose, rate of

infusion, and endpoint/purpose of the study, the ketamine infusions did not fall into the category of 'moderate sedation' and thus no cardiac monitoring was required at our institution. Severity of depressive symptoms (MADRS), psychotomimetic, and dissociative effects were measured 30 min before infusion. Psychomimetic symptoms were measured by the four-item positive symptom subscale of the Brief Psychiatric Rating Scale (BPRS+) (Overall, 1962) (scale range 4–28) consisting of suspiciousness, hallucinations, unusual thought content, and conceptual disorganization; dissociative effects were measured with the Clinician-Administered Dissociative States Scale (CADSS) (Bremner et al., 1998) (scale range 0–92).

Subjects then received IV infusion of 0.5 mg/Kg of ketamine hydrochloride solution (Mylan Inc., USA) over 40 min. The dose of ketamine was determined by ideal body weight based on sex, age, height, and body frame in the Metropolitan Life Insurance tables (www.halls.md/ideal-weight/body). MADRS, BPRS+, and CADSS were measured at the end of infusion (t_0+40 min) and again at t_0+100 and t_0+160 min. The sleep and appetite item scores on the MADRS were kept the same as those obtained before infusion as there was no expectation of change. All subjects were monitored at least for 2 h post infusion. Before leaving the infusion unit accompanied by a competent adult, subjects were administered the modified Aldrete scoring system (Aldrete, 1995) to demonstrate by obtaining a score ≥ 9 that all clinically significant ketamine side effects were resolved. The mAldrete is a set of criteria commonly used to assess transition from anesthesia to recovery and takes into account activity, respiration, circulation, consciousness, and SpO2 level to compose a final score.

Procedures for the subsequent infusions at days 3, 5, 8, 10, and 12 were identical to those of the first infusion. Those patients that achieved response after completion of six ketamine were followed weekly for 4 wk to measure depressive symptoms by MADRS rating scores. Subjects continued with same stable dose of antidepressant regimen during the course of infusions and follow-up visits. In case that relapse occurred, subsequent mental care was managed by her clinician to change or add medications if needed.

Neurocognitive assessment

All participants completed a 2-h battery of cognitive tests at baseline and at each follow-up visit. The neurocognitive testing was selected from the CogState battery (www.cogstate.com) (Collie et al., 2003a). For each test within this battery, the stimuli consisted of playing cards. Tasks were designed to test attention, memory (working, visual, and verbal), speed of processing, and set shifting. The tests were selected because of their brevity, demonstrated utility for within-subjects experimental designs, for the parametric properties of their outcome

measures, and their use in psychopharmacology trials (Snyder et al., 2005; Falletti et al., 2006). Furthermore, the CogState battery can be administered repeatedly using many alternate forms and still acceptable test-retest reliability without generating significant practice effects (Collie et al., 2003b; Falletti et al., 2006). The neurocognitive tasks were administered in a fixed sequence presented on laptop computers in a quiet room to minimize distracting noise. Responses were indicated by pressing keys on the laptop or using a computer mouse if preferred. Brief descriptions of the tasks are provided in Table 1 with further details to be found elsewhere (Maruff et al., 2009; Fredrickson et al., 2010).

Each of these cognitive tasks yields multiple outcome measures. We selected a single primary outcome from each test in the battery that has been shown to be optimal for the detection of change as it contains only a small probability of floor or ceiling effects and no restriction in the range of possible performance values. The outcome measures are normally distributed or corrected to normality through the use of mathematical transformation (e.g. logarithmic base 10, or square root arcsine proportion correct).

Data analysis

Linear mixed models using maximum likelihood estimation and an unstructured covariance structure were used to analyze change in MADRS scores over time, examining both simple change and change controlling for baseline cognitive measures. Mixed models were also used to examine change in neurocognitive performance over time. In all models assessing change over time both the intercept and time were random effects with intercept, time and other covariates, depending on specific analysis, as fixed effects. Finally, logistic regression models were employed to examine the effects of change in neurocognitive performance as predictors of depression relapse following treatment. As the analysis on cognitive performance was exploratory, the study was not powered to detect differences in this matter.

Results

Demographic and clinical characteristics

Demographics and baseline characteristics of the study sample are presented in Table 2. All 15 patients were male; 14 were Caucasians. On average, the sample age was 52 years, had 15 years of education, were chronically depressed with onset of first MDE at age 32, had at least three lifetime episodes of major depression, and presented moderate to severe symptoms of depression (17-item HDRS mean score=20.3, s.d.: 4.3) during a current episode of 17 months. Eleven subjects had at least one first degree relative with mood disorder; three had a past history of substance disorder; 11 had at least one

Table 1. Description of neurocognitive domains measured at baseline and at follow-up visits after six ketamine infusions

Neurocognitive function	Cognitive task	Objective	Outcome	Measure type	Range of values for the variable
Attention	Identification Task (IDN)	Identify whether the card presented is red	Transformed reaction times for correct responses. (Lower score=better performance)	Speed	2 to 5
Working memory	One Back Task (ONB) (Simple working memory)	Identify whether a card is the same to the one just before	Transformed proportion of correct responses. (Higher score=better performance)	Accuracy	0 to 1.57
	Two Back Task (TWOB) (Complex working memory)	Identify whether a card is the same to the one two cards before	Transformed proportion of correct responses. (Higher score=better performance)	Accuracy	0 to 1.57
	Groton Maze Learning Test (GML) (Spatial working memory)	Find the hidden pathway in a 10×10 grid of tiles	Total number of errors made in attempting to learn the same hidden pathway on five consecutive trials at a single session. (Lower score=better performance)	Accuracy	0 to infinity
Visual memory	Continuous Paired Associate Learning Task (CPAL)	Find the correct location of the object	Total number of errors across five rounds. (Lower score=better performance)	Accuracy	0 to infinity
	One Card Learning Task (OCL)	Identified whether a card has been seen before in the task	Transformed proportion of correct responses. (Higher score=better performance)	Accuracy	0 to 1.57
	Groton Maze Learning Test - Delayed Recall (GMR)	Remember the hidden pathway learned previously in a 10×10 grid of tiles	Total number of errors made in remembering the maze pathway after a delay. (Lower score=better performance)	Accuracy	0 to infinity
Verbal memory	International Shopping List Task (ISL)	Remember items read from a shopping list	Total number of correct responses made in remembering the list on three consecutive trials at a single session. (Higher score=better performance)	Accuracy	0 to infinity
	International Shopping List Task: Delayed Recall (ISRL)	Remember items from previously read shopping list	Total number of correct responses made in remembering the list after a delay. (Higher score=better performance)	Accuracy	0 to infinity
Speed of processing	Groton Maze Chase Test (GMCT)	Chase the target in a 10×10 grid of tiles	The total number of correct moves made per second. (Higher score=better performance)	Accuracy	0.01 to infinity
	Detection Task (DET)	Identify once the a card is flipped over and face up	Mean of transformed reaction times for correct responses. (Lower score=better performance)	Speed	2 to 5
Set shifting	Set-Shifting Task (SETS)	Identify whether a card is the target stimulus dimension (a color or a number).	Total number of errors across five rounds. (Lower score=better performance)	Accuracy	0 to infinity

Table 2. Demographic and clinical characteristics of patients with treatment-resistant depression

Characteristics	#1	#2	#3	#4	#5	#6	#7	#8	#9	#10	#11	#12	#13	#14	#15
Age	28	55	69	52	32	41	66	67	57	53	64	62	69	43	23
Gender, male/female	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male
Education, years	14	14	23	14	14	17	19	14	14	12	13	14	18	14	14
First degree relative with mood disorder, yes/no	No	No	Yes	Yes	Yes	No	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes
Psychiatric hospitalizations, no	0	1	2	5	0	0	1	3	3	1	1	2	1	0	7
Past substance disorder, yes/no	No	No	No	No	Yes	No	No	No	No	No	Yes	No	No	Yes	No
History of suicide attempts, yes/no	No	No	No	Yes	No	No	No	No	No	No	Yes	Yes	No	Yes	No
History of ECT, yes/no	No	Yes	No	No	No	No	No	Yes	No	No	No	No	No	No	No
Lifetime MDD episodes, no	2	3	3	5	5	3	3	3	2	3	3	6	2	5	10
Age at onset of first MDE, years	22	42	35	31	16	34	30	45	54	43	22	52	18	27	14
Length of current episode, months	18	24	9	9	7	12	36	15	36	20	9	15	24	9	5
Baseline HDRS score	19	18	23	16	17	19	18	19	25	14	18	18	28	27	26
Baseline MADRS score	29	22	23	31	35	26	27	40	39	24	36	24	24	33	36
MMSE score	29	30	30	29	29	30	29	30	28	28	28	30	30	27	27
Baseline CGI score	5	5	5	5	5	5	5	6	5	4	6	4	5	5	5
Failed antidepressants during current episode, no	3	3	4	3	3	3	3	3	3	3	3	3	3	4	5

psychiatric hospitalization; four had prior suicidal attempts; and two had received electroconvulsive therapy for depression.

Out of 15 subjects enrolled in the study, one dropped out after the first infusion owing to decreased energy and increased irritability, and another patient dropped out after two infusions owing to dissatisfaction with the expected therapeutic effect from ketamine. Analysis for the neurocognitive effects of serial ketamine infusions during follow-up and possible association with relapse from antidepressant response was limited to those 13 patients that completed six ketamine infusions.

Antidepressant outcomes

For the sample of 13 subjects, the within-subject change in MADRS score over six ketamine infusions was statistically significant ($F(5, 65)=37.8$, $p<0.0001$) where the severity of depressive symptoms at baseline (mean MADRS score=29.9, $s.d.=2.3$) decreased after the last infusion (mean MADRS score=7.0, $s.d.=2.3$). Out of 13 subjects who completed all six infusions, 12 (92.3%) achieved response criterion and nine (69.2%) remitted. After the first infusion, three subjects responded (23%) and one subject remitted (7.7%). Seven subjects reached response and six remitted after receiving three or more infusions.

Of the 12 patients who responded after six infusions, MADRS scores were obtained weekly for 4 wk. Five out of eleven subjects remained in response status throughout the four weeks of follow-up. The mean time for those six subjects who relapsed after the last ketamine infusion was 16 d (range 7–28 d). Four patients relapsed within one week after the last infusion.

Baseline neurocognitive performance predicts change of MADRS over six ketamine infusion

We conducted a linear mixed model analysis with MADRS change score over time from baseline as the dependent variable and baseline neurocognitive tasks, age, onset of first MDE, duration of current depressive episode, family history of mood or substance use disorder, and lifetime number of MDE as predictor variables. Performance in attention at baseline and age at onset of MDE were significant predictors of change in severity of depressive symptoms over six infusions. The likelihood of response through six ketamine infusions was greater among depressed subjects with lower attention at baseline ($F(1,13)=5.59$, $p=0.034$) and younger age of onset of MDE ($F(1,13)=4.853$, $p=0.046$). Verbal memory scores at baseline was a marginally significant predictor of change in MADRS score over time ($F(1,13)=3.40$, $p=0.080$) where better performance increased the likelihood of improvement from depression through repeated ketamine treatment.

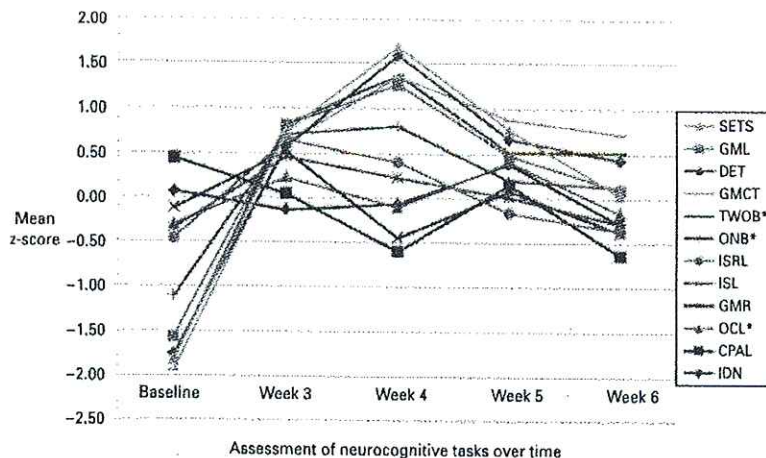


Fig. 1. Short-term effects of repeated ketamine on neurocognition among treatment-resistant depression (TRD) subjects. Mean z-score of neurocognitive tasks at baseline and at follow-up visits post-ketamine treatment among subjects with TRD. Attention: Identification Task (IDN). Working Memory: One Back Task (ONB); Two Back Task (TWOB); Groton Maze Learning Test (GML). Visual Memory: Continuous Paired Associate Learning Task (CPAL); One Card Learning Task (OCL); Groton Maze Learning Test – Delayed Recall (GMR). Verbal Memory: International Shopping List Task (ISL); International Shopping List Task: Delayed Recall (ISRL). Speed of Processing: Groton Maze Chase Test (GMCT); Detection Task (DET). Set shifting: Set-Shifting Task (SETS). * $p < 0.05$.

Neurocognitive effects of six ketamine infusions

There were significant changes in repeated neurocognitive performance over time after completion of six ketamine infusions (Fig. 1). Significant improvement was found in scores of visual memory (One Card Learning Task) ($F(4, 33.82) = 5.12$, $p = 0.002$), simple working memory (One Back Task) ($F(4, 24.85) = 3.29$, $p = 0.027$) and complex working memory and (Two Back Task) ($F(4, 32.76) = 4.18$, $p = 0.008$) after last ketamine infusion compared to baseline. Other cognitive tasks showed non-significant changes after repeated ketamine infusions (data not shown) with scores showing improvement or not change in cognitive performance from baseline.

We also analyzed whether changes in cognitive tasks after the last ketamine infusion were related to changes in depressive symptoms. When MADRS scores were considered as a covariate, non-significant changes over time were found in visual memory ($F(1, 2.39) = 0.08$, $p = 0.797$) and in both simple and complex working memory ($F(1, 2.71) = 0.013$, $p = 0.917$ and $F(1, 3.13) = 2.19$, $p = 0.230$), respectively).

Neurocognitive performance change after completion of six ketamine infusions

By performing logistic regression analysis, we examined whether changes in neurocognition after completing six ketamine infusions were associated to the likelihood of relapse (defined as MADRS > 50% of baseline score) ascertained during subsequent follow-up visits. There was no significant association between changes in scores of neurocognitive testing with chances of relapse at

follow-up. Antidepressant outcome as a continuous variable measured by MADRS scores showed similar results.

Discussion

In this open label trial of repeated ketamine infusions for TRD, we found that improvement of depressive symptoms was associated with lower attention at baseline. Completion of six ketamine infusions produced changes in neurocognitive performance through 4 wk of follow-up; this was accounted for by improvement in the severity of depressive symptom over time. Finally, the acute neurocognitive effect of repeated ketamine infusions was not associated with the likelihood of subsequent relapse during the short-term follow-up.

Murrough and colleagues (Murrough et al., 2013b) found that responders to a single ketamine infusion had poorer baseline neurocognitive performance relative to non-responders and, in particular, slower processing speed. Similarly, the current study found that depressed subjects with lower attention at baseline had greater chances to decrease the severity in depressive symptoms during six ketamine infusions. Previous studies on cognitive functions and response to traditional antidepressants, however, have shown results in the opposite direction. For instance, the depression executive dysfunction (DED) model proposes that cognitive impairment, particularly executive dysfunction, is associated with poor response to antidepressant medication in older patients (Alexopoulos et al., 2005). Lower performance in non-executive cognitive functions such as visuo-spatial construction, memory, and processing speed were also

associated with poorer antidepressant response in some populations (McLennan and Mathias, 2010). Whether these discrepancies are related to ketamine's mechanism of action different from traditional antidepressants will need to be substantiated by further studies.

The current study revealed that serial infusions of ketamine in TRD were not associated with cognitive decline at least in the short-term (4 wk). Whereas Murrough and colleagues (Murrough et al., 2013b) revealed a selective impairment in delayed recall 40 min after a single ketamine infusion in TRD subjects, more recently, Diamond and colleagues (Diamond et al., 2014) examined the effect of repeated ketamine infusions on objective (autobiographical, episodic, and semantic) and subjective memory by conducting an open-label naturalistic study among bipolar and unipolar TRD patients. In contrast to our study, Diamond et al. treated over 3 wk with either three or six ketamine infusion a mixed group of bipolar and unipolar TRD patients. The performance on memory tests was measured 4–7 d as well as 12 and 26 wk after the last infusion. Diamond's study found no memory deficits after completion of repeated ketamine providing further support to the current study regarding safety aspects of neurocognitive effect of ketamine in TRD. As Diamond et al. pointed out, 'higher frequency, higher doses or longer duration of ketamine infusions could potentially cause cognitive problems' and justified further examination.

The NMDA receptor is critical in a form of synaptic plasticity called long-term potentiation (LTP) which is central for learning and memory (Bliss and Collingridge, 1993). Given the principal action of ketamine is at the NMDA receptor, the immediate effect of ketamine use on cognition have been widely investigated. The most robust finding is that a single dose of ketamine induced marked, dose-dependent impairments in working and episodic memory in healthy subjects, which would impact profoundly on users' ability to function (Fletcher and Honey, 2006; Morgan and Curran, 2006). Deficits in other types of memory such as verbal and semantic memory (Hartvig et al., 1995; Adler et al., 1998; LaPorte et al., 2005; Parwani et al., 2005) as well as attention (Malhotra et al., 1996) and executive function (Krystal et al., 1994a) have also been reported.

The long-term neurocognitive adverse events of ketamine are scarce in the literature where data essentially derived from studies in ketamine drug users. Overall, recreational use defined as average use of 3 d per month, was not associated with impaired cognitive function (Morgan et al., 2009). Similarly, infrequent use (less than four times a week but at least once a month) (Morgan et al., 2009) does not appear to be associated with long-term cognitive impairment. However, frequent ketamine users (more than four times a week) appear to exhibit profound impairments in both short- and long-term memory (Morgan et al., 2012).

Whether memory impairment by heavy ketamine use might abate after cessation of use is unclear. Jansen

(Jansen, 1990) described a case in which a subject had persisting impaired recall and attention and a subtle visual anomaly after cessation of long-term high-dose ketamine use. On the contrary, Morgan et al. (Morgan et al., 2009) found in a group of 30 ex-ketamine users who had been abstinent for at least a year that memory impairments may be reversible when individuals stop using the drug. The reversibility of cognitive impairments is supported by reversible neurotoxic effects observed in animals that have been exposed to chronic and high doses of NMDA-receptor antagonists (Popke et al., 2001).

Similar to findings in memory deficits, frequent ketamine user may also show impairments in some aspects of executive functions such as verbal fluency and planning (Morgan et al., 2009). Ketamine has shown to modulate dopamine transmission in the dorsolateral prefrontal cortex (Moghaddam et al., 1997), a system critically involved in working memory and executive functions (Krystal et al., 2005). In fact, chronic recreational ketamine users with no significant performance differences with healthy controls exhibited a regionally selective up-regulation of dopamine 1 (D1) receptor availability in the dorsolateral prefrontal cortex (Narendran et al., 2005). This up-regulation might be an early sign of system dysregulation suggesting a compensating mechanism to dopaminergic deficit in the prefrontal region induced by NMDA antagonist exposure.

The significances of our findings should be evaluated in the scope of the study limitations. The number of subjects is small, all males, and several exclusion criteria were applied. Study results then should be confirmed by larger samples that include sub-populations of TRD subjects (e.g. psychiatric comorbidity) and clinical variables that might modify respond to repeated ketamine infusions. For instance, levels of anxiety were not included in the study. The association between a family history of alcohol abuse and antidepressant response to ketamine previously reported (Phelps et al., 2009; Luckenbaugh et al., 2012) was not confirmed in this study. Future randomized placebo-control studies will be required to determine specificity from findings suggested from this single-arm, open-label design study.

Although we intended to assess the short-term neurocognitive effects after administration of six ketamine infusions, it is not known whether the frequency and the length of continuing treatment (e.g. maintenance) would cause temporary or permanent cognitive deficits, if any. Electroconvulsive therapy, the oldest and most effective treatment for TRD at present (UK ECT Review Group, 2003) might cause persistent cognitive deficits especially in retrograde amnesia of autobiographical information following acute treatment (Rami-Gonzalez et al., 2001; Rejsner, 2003; Verwijk et al., 2012). Based on studies on ketamine drug users and neurocognition, the frequency of ketamine administration could be a source of concern when evaluating ketamine risk/benefits as a safe intervention for TRD.

In conclusion, our study revealed association between baseline neurocognitive performance in attention task and the likelihood of antidepressant improvement through a series of ketamine infusions. Most importantly, the study suggested the virtually lack of short-term neurocognitive effect after completion of six ketamine infusions in TRD. Future studies will be required to determine whether neurocognitive side effects will prevent further consideration of ketamine as a possible intervention for refractory depression.

Acknowledgments

Dr Shiroma was supported by the Minneapolis VA Center for Epidemiological and Clinical Research (CECR), a VA Clinical Research Center of Excellence, and the Mental Health Service Line, Minneapolis VA Medical Center. The funding source had no further role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication. We are extremely grateful to the staff from Special Diagnostic and Treatment Unit (SDTU) at the Minneapolis VAMC for their support during the conduction of the study.

Statement of Interest

None

References

- Adler CM, Goldberg TE, Malhotra AK, Pickar D, Breier A (1998) Effects of ketamine on thought disorder, working memory, and semantic memory in healthy volunteers. *Biol Psychiatry* 43:811–816.
- Aldrete JA (1995) The post-anesthesia recovery score revisited. *J Clin Anesth* 7:89–91.
- Alexopoulos GS, Kiess DN, Heo M, Murphy CF, Shanmugham B, Gunning-Dixon F (2005) Executive dysfunction and the course of geriatric depression. *Biol Psychiatry* 58:204–210.
- Bliss TV, Collingridge GL (1993) A synaptic model of memory: long-term potentiation in the hippocampus. *Nature* 361:31–39.
- Bremner JD, Krystal JH, Putnam FW, Southwick SM, Marmar C, Charney DS, Mazure CM (1998) Measurement of dissociative states with the clinician-administered dissociative states scale (CADSS). *J Trauma Stress* 11:125–136.
- Collie A, Maruff P, Darby DG, McStephen M (2003a) The effects of practice on the cognitive test performance of neurologically normal individuals assessed at brief test-retest intervals. *J Int Neuropsychol Soc* 9:419–428.
- Collie A, Maruff P, Darby DG, McStephen M (2003b) The effects of practice on the cognitive test performance of neurologically normal individuals assessed at brief test-retest intervals. *J Int Neuropsychol Soc* 9:419–428.
- Corsen G, Oget S, Reed PC (1971) Computerized evaluation of psychic effects of ketamine. *Anesth Analg* 50:397–401.
- Diamond PR, Farmery AD, Atkinson S, Haldar J, Williams N, Cowen PJ, Geddes JR, McShane R (2014) Ketamine infusions for treatment resistant depression: a series of 28 patients treated weekly or twice weekly in an ECT clinic. *J Psychopharmacol* 6:536–544.
- Falletti MG, Maruff P, Collie A, Darby DG (2006) Practice effects associated with the repeated assessment of cognitive function using the CogState battery at 10-minute, one week and one month test-retest intervals. *J Clin Exp Neuropsychol* 28:1095–1112.
- First MB, Spitzer RL, Gibbon M, Williams JBW (1996) Structured clinical interview for DSM-IV axis I disorders, clinician version (SCID – CV). Washington, DC: American Psychiatric Press.
- Fletcher PC, Honey GD (2006) Schizophrenia, ketamine and cannabis: evidence of overlapping memory deficits. *Trends Cogn Sci* 10:167–174.
- Folstein MF, Folstein SE, McHugh PR (1975) “Mini-mental state”. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 12:189–198.
- Fredrickson J, Maruff P, Woodward M, Moore L, Fredrickson A, Sach J, Darby D (2010) Evaluation of the usability of a brief computerized cognitive screening test in older people for epidemiological studies. *Neuroepidemiology* 34:65–75.
- Green SM, Li J (2000) Ketamine in adults: what emergency physicians need to know about patient selection and emergence reactions. *Acad Emerg Med* 7:278–281.
- Hamilton M (1960) A rating scale for depression. *J Neurol Neurosurg Psychiatry* 23:56–62.
- Hartvig P, Valtysson J, Lindner KJ, Kristensen J, Karlsten R, Gustafsson LL, Persson J, Svensson JO, Oye I, Antoni G (1995) Central nervous system effects of subdissociative doses of (S)-ketamine are related to plasma and brain concentrations measured with positron emission tomography in healthy volunteers. *Clin Pharmacol Ther* 58:165–173.
- Jansen KL (1990) Ketamine-can chronic use impair memory? *Int J Addict* 25:133–139.
- Krystal JH, Karper LP, Seibyl JP, Freeman GK, Delaney R, Bremner JD, Heninger GR, Bowers MB Jr., Charney DS (1994a) Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. psychotomimetic, perceptual, cognitive, and neuroendocrine responses. *Arch Gen Psychiatry* 51:199–214.
- Krystal JH, Karper LP, Seibyl JP, Freeman GK, Delaney R, Bremner JD, Heninger GR, Bowers MB Jr., Charney DS (1994b) Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. psychotomimetic, perceptual, cognitive, and neuroendocrine responses. *Arch Gen Psychiatry* 51:199–214.
- Krystal JH, Perry EB Jr., Gueorguieva R, Belger A, Madonick SH, Abi-Dargham A, Cooper TB, Macdougall L, Abi-Saab W, D’Souza DC (2005) Comparative and interactive human psychopharmacologic effects of ketamine and amphetamine: implications for glutamatergic and dopaminergic model psychoses and cognitive function. *Arch Gen Psychiatry* 62:985–994.
- LaPorte DJ, Blaxton TA, Michaelidis T, Robertson DU, Weiler MA, Tamminga CA, Lahti AC (2005) Subtle effects of ketamine on memory when administered following stimulus presentation. *Psychopharmacology (Berl)* 180:385–390.
- Luckenbaugh DA, Ibrahim L, Brutsche N, Franco-Chaves J, Mathews D, Marquardt CA, Cassarly C, Zarate CA Jr. (2012) Family history of alcohol dependence and antidepressant response to an N-methyl-D-aspartate antagonist in bipolar depression. *Bipolar Disord* 14:880–887.

- Malhotra AK, Pinals DA, Weingartner H, Sirocco K, Missar CD, Pickar D, Breier A (1996) NMDA receptor function and human cognition: the effects of ketamine in healthy volunteers. *Neuropsychopharmacology* 14:301–307.
- Maruff P, Thomas E, Cysique L, Brew B, Collie A, Snyder P, Pietrzak RH (2009) Validity of the CogState brief battery: relationship to standardized tests and sensitivity to cognitive impairment in mild traumatic brain injury, schizophrenia, and AIDS dementia complex. *Arch Clin Neuropsychol* 24:165–178.
- McLennan SN, Mathias JL (2010) The depression-executive dysfunction (DED) syndrome and response to antidepressants: a meta-analytic review. *Int J Geriatr Psychiatry* 25:933–944.
- Moghaddam B, Adams B, Verma A, Daly D (1997) Activation of glutamatergic neurotransmission by ketamine: a novel step in the pathway from NMDA receptor blockade to dopaminergic and cognitive disruptions associated with the prefrontal cortex. *J Neurosci* 17:2921–2927.
- Montgomery SA, Asberg M (1979) A new depression scale designed to be sensitive to change. *Br J Psychiatry* 134:382–389.
- Moretti RJ, Hassan SZ, Goodman LI, Meltzer HY (1984) Comparison of ketamine and thiopental in healthy volunteers: effects on mental status, mood, and personality. *Anesth Analg* 63:1087–1096.
- Morgan CJ, Curran HV (2006) Acute and chronic effects of ketamine upon human memory: a review. *Psychopharmacology (Berl)* 188:408–424.
- Morgan CJ, Mofeez A, Brandner B, Bromley L, Curran HV (2004) Acute effects of ketamine on memory systems and psychotic symptoms in healthy volunteers. *Neuropsychopharmacology* 29:208–218.
- Morgan CJ, Muetzelfeldt L, Curran HV (2009) Ketamine use, cognition and psychological wellbeing: a comparison of frequent, infrequent and ex-users with polydrug and non-using controls. *Addiction* 104:77–87.
- Morgan CJ, Curran HV, Independent Scientific Committee on Drugs (2012) Ketamine use: a review. *Addiction* 107:27–38.
- Murrough JW, Perez AM, Pillemer S, Stern J, Parides MK, aan het Rot M, Collins KA, Mathew SJ, Charney DS, Iosifescu DV (2013a) Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. *Biol Psychiatry* 74:250–256.
- Murrough JW, Wan LB, Iacoviello B, Collins KA, Solon C, Glicksberg B, Perez AM, Mathew SJ, Charney DS, Iosifescu DV, Burdick KE (2013b) Neurocognitive effects of ketamine in treatment-resistant major depression: association with antidepressant response. *Psychopharmacology (Berl)* 11 Sept. 2013 (Epub ahead of print).
- Narendran R, Frankle WG, Keefe R, Gil R, Martinez D, Slifstein M, Kegeles LS, Talbot PS, Huang Y, Hwang DR, Khenissi L, Cooper TB, Laruelle M, Abi-Dargham A (2005) Altered prefrontal dopaminergic function in chronic recreational ketamine users. *Am J Psychiatry* 162:2352–2359.
- Overall JGDR., (1962) The brief psychiatric rating scale. *Psychol Rep* 10:799–812.
- Parwani A, Weiler MA, Blaxton TA, Warfel D, Hardin M, Frey K, Lahti AC (2005) The effects of a subanesthetic dose of ketamine on verbal memory in normal volunteers. *Psychopharmacology (Berl)* 183:265–274.
- Perry EB Jr., Cramer JA, Cho HS, Petrakis IL, Karper LP, Genovese A, O'Donnell E, Krystal JH, D'Souza DC, Yale Ketamine Study Group (2007) Psychiatric safety of ketamine in psychopharmacology research. *Psychopharmacology (Berl)* 192:253–260.
- Phelps LE, Brutsche N, Moral JR, Luckenbaugh DA, Manji HK, Zarate CA Jr. (2009) Family history of alcohol dependence and initial antidepressant response to an N-methyl-D-aspartate antagonist. *Biol Psychiatry* 65:181–184.
- Popke EJ, Allen RR, Pearson EC, Hammond TG, Paule MG (2001) Differential effects of two NMDA receptor antagonists on cognitive-behavioral performance in young nonhuman primates II. *Neurotoxicol Teratol* 23:333–347.
- Rami-Gonzalez L, Bernardo M, Boget T, Salamero M, Gil-Verona JA, Junque C (2001) Subtypes of memory dysfunction associated with ECT: characteristics and neurobiological bases. *J Ect* 17:129–135.
- Rasmussen KG, Lineberry TW, Galaray CW, Kung S, Lapid MI, Palmer BA, Ritter MJ, Schak KM, Sola CL, Hanson AJ, Frye MA (2013) Serial infusions of low-dose ketamine for major depression. *J Psychopharmacol* 27:444–450.
- Reisner AD (2003) The electroconvulsive therapy controversy: evidence and ethics. *Neuropsychol Rev* 13:199–219.
- Sackeim HA (2001) The definition and meaning of treatment-resistant depression. *J Clin Psychiatry* 62 (Suppl. 16):10–17.
- Shiroma PR, Johns B, Kuskowski M, Wels J, Thuras P, Albott CS, Lim KO (2014) Augmentation of response and remission to serial intravenous subanesthetic ketamine in treatment resistant depression. *J Affect Disord* 155:123–129.
- Snyder PJ, Werth J, Giordani B, Caveney AF, Feltner D, Maruff P (2005) A method for determining the magnitude of change across different cognitive functions in clinical trials: the effects of acute administration of two different doses alprazolam. *Hum Psychopharmacol* 20:263–273.
- UK ECT Review Group (2003) Efficacy and safety of electroconvulsive therapy in depressive disorders: a systematic review and meta-analysis. *Lancet* 361:799–808.
- Verwijk E, Comijs HC, Kok RM, Spaans HP, Stek ML, Scherder EJ (2012) Neurocognitive effects after brief pulse and ultrabrief pulse unilateral electroconvulsive therapy for major depression: a review. *J Affect Disord* 140:233–243.